

## Inhibition of tryptophan hydroxylase activity and decreased 5-HT<sub>1A</sub> receptor binding in a mouse model of Huntington's disease

George J. Yohrling IV,\* George C.-T. Jiang,† Molly M. DeJohn,\* Daniel J. Robertson,‡  
Kent E. Vrana‡ and Jang-Ho J. Cha\*

\*Department of Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, USA

†Molecular Genetics Program, ‡Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

### Abstract

The pathogenic mechanisms of the mutant huntingtin protein that cause Huntington's disease (HD) are unknown. Previous studies have reported significant decreases in the levels of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the brains of the R6/2 transgenic mouse model of HD. In an attempt to elucidate the cause of these neurochemical perturbations in HD, the protein levels and enzymatic activity of tryptophan hydroxylase (TPH), the rate-limiting enzyme in 5-HT biosynthesis, were determined. Enzyme activity was measured in brainstem homogenates from 4-, 8-, and 12-week-old R6/2 mice and compared with aged-matched wild-type control mice. We observed a 62% decrease in brainstem TPH activity ( $p = 0.009$ ) in 4-week-old R6/2 mice, well before the onset of behavioral symptoms. In addition, significant decreases in TPH activity were also observed at 8 and 12 weeks of age (61%,  $p = 0.02$  and 86%,  $p = 0.005$ , respectively). In the 12-week-old-mice, no change in immunoreactive TPH was observed. *In vitro* binding showed

that TPH does not bind to exon 1 of huntingtin in a polyglutamine-dependent manner. Specifically, glutathione-S-transferase huntingtin exon 1 proteins with 20, 32 or 53 polyglutamines did not interact with radiolabeled tryptophan hydroxylase. Therefore, the inhibition of TPH activity does not appear to result from a direct huntingtin/TPH interaction. Receptor binding analyses for the 5-HT<sub>1A</sub> receptor in 12-week-old R6/2 mice revealed significant reductions in 8-OH-[<sup>3</sup>H]DPAT binding in several hippocampal and cortical regions. These results demonstrate that the serotonergic system in the R6/2 mice is severely disrupted in both pre-symptomatic and symptomatic mice. The presymptomatic inhibition of TPH activity in the R6/2 mice may help explain the functional consequences of HD and provide insights into new targets for pharmacotherapy.

**Keywords:** brainstem, GST pull-down, Huntington's disease, receptor binding, serotonin, tryptophan hydroxylase.

*J. Neurochem.* (2002) **82**, 1416–1423.